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Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily clinical practice?

Gwen MC Masclee^{1,2}, Vera E Valkhoff^{1,2}, Eva M van Soest¹, René Schade¹, Giampiero Mazzaglia³, Mariam Molokhia⁴, Gianluca Trifirò^{1,5}, Jay L Goldstein⁶, Sonia Hernández-Díaz⁷, Ernst J Kuipers^{2,8}, and Miriam C J M Sturkenboom^{1,9}

¹Department of Medical Informatics, Erasmus University Medical Centre, Rotterdam, The Netherlands. ²Department of Gastroenterology and Hepatology, Erasmus University Medical Centre, Rotterdam, The Netherlands. ³Health Search, Italian College of General Practitioners, Florence, Italy. ⁴Primary Care & Public Health Sciences, Kings College London, London, United Kingdom. ⁵Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy. ⁶Department of Medicine, Division of Gastroenterology, NorthShore University HealthSystem, Evanston, Illinois, USA. ⁷Department of Epidemiology, Harvard School of Public Health, Boston, USA. ⁸Department of Internal Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands. ⁹Department of Epidemiology, Erasmus University Medical Centre, Rotterdam, The Netherlands.

Summary

Background—Two strategies for prevention of upper gastrointestinal (UGI) events for non-selective (ns)NSAID users are replacement of the nsNSAID by a cyclo-oxygenase-2-selective inhibitor (coxib) or co-prescription of a gastroprotective agent (GPA).

Aim—To identify whether and in whom either of these strategies should be preferred in daily practice.

Methods—A nested case-control study was conducted using three European primary care databases. We selected a cohort including all naive nsNSAID+GPA (< 80% GPA adherence) and coxib users (without GPA use) aged < 50 years. Cases with an UGI event (i.e. symptomatic UGI ulcer or bleeding (UGIB)) were matched to cohort members without an UGI event on age, sex and number of individual UGI risk factors (i.e. UGI event history, age > 65 years, concomitant use of anticoagulants, antiplatelets, or glucocorticoids) and calendar time. Conditional logistic regression analysis was used to calculate odds ratios (ORs) with 95% confidence intervals (CI), while adjusting for potential confounders.

Results—Within the NSAID cohort (n=617,220), 398 UGI cases were identified. The risk of UGI events was equivalent for coxib and nsNSAID+GPA (< 80% adherence) users (OR: 1.02; 95%CI:0.77-1.37). In concurrent glucocorticoid users, the risk of UGI events was significantly elevated for nsNSAID+GPA (< 80% adherence) compared to coxib users (OR: 9.01; 95%CI: 1.61-50.50).

Conclusions—The risk of UGI events was similar in nsNSAID+GPA (< 80% adherence) and coxibs users. In patients concurrently using glucocorticoids a significant increase in the risk of UGI events for nsNSAID+GPA users was observed and coxibs should be preferred.

Keywords

Cyclo-oxygenase-2 inhibitors; non-selective nonsteroidal anti-inflammatory drugs; symptomatic UGI events; gastroprotection

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed by both general practitioners and medical specialists, and serve as key pharmacological agents in the management of arthralgic and inflammatory conditions. Multiple epidemiologic studies and prospective clinical outcome trials have characterized the risk of NSAID-related gastrointestinal (GI) complications, which include upper gastrointestinal (UGI) ulcers and bleeding. To mitigate the increased risk among long term NSAID users, guidelines have been developed and strategies are recommended¹⁻⁴ including prescription of cyclo-oxygenase (COX)-2-selective inhibitors (coxibs) or concurrent use of gastroprotective agents (GPAs), such as proton pump inhibitors (PPIs). Although both preventive strategies aim to reduce the incidence of UGI events, the risk of such complications is not eliminated; a considerable proportion of NSAID plus GPA users (6.3-8.5%) and coxib users (3.7-8.9%) continues to experience UGI events.⁵⁻⁸ Defining which of the two preventive strategies is preferred in terms of UGI safety has been the scope of recent studies. Most of the randomized clinical trials showed no superiority for one of the preventive strategies over the other.^{5-7,9} Only one large randomized clinical trial showed a beneficial effect in favor of celecoxib. In this 6 month trial patients randomized to celecoxib, as compared to the combination of diclofenac and omeprazole, had a reduced rate of clinically significant overall gastrointestinal events when a composite endpoint was considered (events from both the upper and lower GI tract). Looking at the upper gastrointestinal tract specifically, this head to head comparison demonstrated similar rates for upper gastrointestinal bleeding.¹⁰ Extrapolation of the previously described body of literature to guide clinicians in the care of the general population has several limitations. Many of the prospective randomized clinical studies have included patients using supra-therapeutic doses of coxibs or included a selected group of high-risk patients (i.e. those with a recent UGI event).^{5-7,10} Alternatively in some of the prospective trials, the presence of co-morbid diseases such as ischemic heart disease, peripheral arterial disease¹⁰, or congestive heart failure⁵ were considered as exclusion criterion, thereby preferentially selecting patients at lower risk of UGI events. Additionally, the exclusion of patients with frequently used co-medication (e.g. low-dose aspirin⁵, anticoagulant agents^{5,7} and corticosteroids⁷) in some of the studies might be an important issue, considering that the use of low-dose aspirin clearly influences the efficacy of UGI protection in coxibs.¹¹⁻¹² Finally, as a consequence of protocol driven inclusion of patients with recent or past UGI bleeding and in some studies, the recruitment of patients from hospital-setting^{5,10} or endoscopy centers⁶⁻⁷, a substantial number of enrolled subjects may have had NSAID-associated complications and as such a higher risk.

Apart from the clinical studies, one population-based cohort study concluded that coxibs alone were not superior to nsNSAID combined with PPI in the prevention of hospitalization for a perforated or bleeding ulcer.¹³ This observation was confirmed in an observational case-control study, using a population-based claims-database in Canada, in which both gastroprotective strategies were similarly effective in the prevention of NSAID-related UGI events, but it did not address the lack of adherence to PPIs.¹⁴ However, we and others have demonstrated that in real life, GPA adherence during nsNSAID use is an important factor to consider when evaluating and comparing the effectiveness of different gastroprotective strategies. If the NSAID and PPI are given as separate medications non- or low adherence to

GPA is often seen¹⁵ and associated with significantly increased risk of nsNSAID-related upper GI events.¹⁶⁻¹⁸

Thus, whether coxibs and nsNSAIDs plus GPA are similarly effective in preventing incident NSAID-related UGI events in daily clinical practice including patients both at high- and low-risk is still unknown. Therefore, we conducted a case-control study to compare the risk of UGI events between coxib users and nsNSAID users, who were highly GPA adherent (at least 80% adherence to GPAs), making use of population-based primary health care data from three European countries. As coxibs might be preferentially prescribed to specific patient groups, we restricted to nsNSAID users who were highly GPA adherent (at least 80% adherence to GPAs).

Materials and Methods

Description of data sources

Three similar European population-based primary care registries served as data sources: 1) the General Practice Research Database (GPRD) from the United Kingdom (UK, 1998–2008), 2) the Integrated Primary Care Information database (IPCI) from the Netherlands (1996–2007), and 3) the Health Search/CSD Longitudinal Patient Database (HSD) from Italy (2000–2007). In these three countries, all citizens are registered with a primary care practice, who acts as a gatekeeper to secondary and tertiary medical care. For each individual patient all relevant medical information from primary and secondary care, as well as additional information, including demographics and drug prescriptions, is recorded in the health care medical record. All three registries comply with European Union guidelines on the use of medical data for research. The protocol of the present study was approved by the Medical Ethics Committee of each database. We have previously shown the validity to combine and to compare data from these databases.^{17, 19} For GPRD, the READ dictionary was used to identify medical diagnosis and symptoms, whereas the International Classification for Primary Care²⁰ and the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)^{21,21} were used for that purpose in IPCI and HSD, respectively. In IPCI and HSD information on drug prescription was coded according to the Anatomical Therapeutic Chemical (ATC) classification.^{22,22} In GPRD information on drugs is captured with MULTILEX product dictionary and British National Formulary (BNF) codes.

Determination of NSAID cohort

The identification of the source population and NSAID cohort has been described elsewhere.¹⁷ In brief, a source population was identified within each database by inclusion of patients from start of the study period, 50 years of age or the date that one year of valid data within the database was available, whichever was the most recent. The one-year period prior to inclusion in the source population was required for valid assessment of baseline characteristics and inclusion and exclusion criteria at the time of NSAID prescription. A cohort of patients who newly started (i.e. no NSAID prescriptions within 6 months prior to inclusion) on either coxibs or nsNSAIDs (excluding the fixed combination of diclofenac with misoprostol) was identified. Exclusion criteria were history of gastrointestinal tract cancer, alcohol abuse, chronic liver disease, inflammatory bowel disease, or coagulopathy. Within the cohort of new users, all episodes of NSAID use were determined and defined as consecutive NSAID prescriptions with intervening gaps not exceeding the duration of the previous NSAID prescription (Figure 1). The duration of an NSAID episode was calculated by dividing the prescribed quantity by daily dose regimen (GPRD/IPCI) or the indication-specific defined daily dose (HSD). The end of an NSAID episode was defined as the end of the duration of the last NSAID prescription within that episode or the end of follow-up, whichever was earliest. All episodes from a patient were eligible for inclusion if the

previous NSAID-prescription ended at least 6 months before the start of the next episode. The density of NSAID use was calculated by the number of NSAID prescription days divided by episode length. Eligible gastroprotective agents (GPAs) were proton pump inhibitors (PPIs), double-dosed histamine₂ receptor antagonists (H₂RAs), and misoprostol.

For the present study, non-selective NSAID users were excluded if they did not use a GPA concomitantly, or if they were non-adherent to the concomitantly used GPA (i.e. coverage of less than 80% of the nsNSAID days). In total, 68.1% of NSAID plus GPA users were highly adherent.¹⁷ The exposure assessment and GPA adherence calculation are schematically depicted in Figure 1. The GPA adherence calculation has been described previously.¹⁸ NSAID episodes during which patients switched between classes of NSAIDs (from nsNSAID to coxib or vice versa) were excluded. Episodes during which coxibs were used concurrently with a GPA were also excluded. Overall, in 83.4% of coxib episodes no GPA was used concomitantly.¹⁹ This resulted in a cohort including only nsNSAID plus GPA (> 80 % adherence) and coxib (alone) users.

Cases and controls selection

Outcomes of interest were a composite of UGI events (including symptomatic ulceration, UGI bleeding (UGIB), perforation or obstruction) and UGIB alone. Identification of the outcomes has been described in more detail elsewhere.¹⁷ The date of outcome (i.e. index date) was determined as date of start of symptoms leading to the diagnosis of the UGI event, or if this date was unknown, date of diagnosis. Events occurring within 60 days after the end of an NSAID episode were attributed to the previous NSAID use.²³

A nested case-control study was conducted. To each case experiencing an UGI event during or within 60 days after the end of an NSAID episode, we matched all control persons from the cohort of the corresponding database. Controls had not experienced any UGI event at the index date of the corresponding case and were at the index date alive, using an NSAID within 60 days prior, had equal number of UGI risk factors (see below) as the case and had similar age (± 3 years) and same gender.

Covariates

We considered as risk factors for UGI events those that are commonly reported in literature: (i) age ≥ 65 years; (ii) a history of UGI events (bleeding/ulceration); (iii) concurrent use of anticoagulants; (iv) concomitant use of antiplatelets (including aspirin ≥ 325 mg/day); and (v) concomitant use of glucocorticoids (equipotent dose of ≥ 5 mg prednisone). Presence of risk factors was determined by electronic searches in all available data prior to or noted at the index date.

Additional potential confounding factors were assessed: dyspepsia in the year before the NSAID episode, (history of) smoking, presence of heart failure or diabetes mellitus, and concomitant use of drugs associated with increased risk of bleeding (selective serotonin reuptake inhibitors (SSRI), spironolactone or calcium antagonists) at the index date.

Statistical analyses

Baseline characteristics of cases and controls were described by database and compared using univariate conditional logistic regression analyses.

To estimate the risk for UGI events and UGI bleeding among nsNSAID + GPA users (> 80% adherence) in comparison to coxib users, matched and adjusted odds ratios (OR) with 95% confidence intervals (CIs) were calculated using conditional logistic regression analyses for each database separately and as pooled analysis. The odds ratio can be interpreted as an

estimate of the relative risk, as person-time is inherently accounted for in the analysis and the underlying source population is representative of the general population.²⁴ The pooling of data across databases was performed by two methods: 1) on patient-level (respecting matched cases and controls from the original database); and 2) on study-level by estimating the risk of UGI events for nsNSAID + GPA (80% adherence) use versus coxib use per database and pooling the three obtained risk estimates using a meta-analytic approach, resulting in an overall risk estimate (inverse variance model) using a random-effects model. The latter method is only appropriate when there is no heterogeneity.

Identification of confounders was performed by entering each potential confounder into the model one by one and were kept in the final model if the risk estimate for the drug exposure changed by more than 10%. As the duration coxibs use might differ from use of nsNSAIDs +GPA (80% adherence) we adjusted also for duration of the episodes and density of NSAID use. Subsequent analyses evaluated the risk of UGI events and UGI bleeding stratified by the presence of individual risk factors: age \geq 65 years, history of UGI event, and use of concomitant medications (antiplatelets, anticoagulants and glucocorticoids). For glucocorticoids, we considered an equipotent dose of prednisone 5 to 10 mg/day as low-dosage; > 10 to 20 mg/day as moderate dosage and >20 mg/day as high-dosage. Multiplicative interaction was tested to identify effect modification by all of the individual UGI risk factors.

All analyses were performed using SPSS 15.0 for Windows (SPSS Inc, Chicago, Ill). Statistical significance was defined as a two-sided p-value<0.05.

Results

Patient characteristics

We identified 384,469 new NSAID users in the United Kingdom (UK), 307 of who experienced an UGI event (194 with UGI bleeding). In the Netherlands 17 cases with an UGI event (14 with UGI bleeding) were identified from 55,004 new users of NSAIDs and in Italy 74 cases with an UGI event (17 with UGI bleeding) were identified from 177,747 new NSAID users. Overall, 57,568 event-free controls were matched to these 398 UGI event cases. Median number of controls was 120 per case (interquartile range: 43-201).

Baseline characteristics of the cases and matched controls are shown in Table 1. In the UK, the most commonly prescribed nsNSAID was ibuprofen (56%), while celecoxib and rofecoxib were the most commonly prescribed coxibs (48% and 40%, respectively). In NL, the most commonly prescribed coxib and nsNSAID were rofecoxib (58%) and diclofenac (52%), respectively. Diclofenac and nimesulide accounted for the greater part of nsNSAIDs in Italy (22% and 25%, respectively), whereas celecoxib (51%) and rofecoxib (41%) were the most frequently prescribed coxibs. Proton pump inhibitors comprised the majority of co-prescribed GPAs in nsNSAID users across countries (UK:99.6%, NL:97.0%, IT:95.8%).

In the UK, UGI event cases reported more often a history of UGI event (OR: 1.50; 95% CI: 1.04-2.16) and used concomitant anticoagulant therapy (OR: 1.85; 95% CI: 1.06-3.25) and SSRIs more frequently (OR: 1.92; 95% CI: 1.33-2.77). In the Netherlands and Italy, UGI event cases were significantly more likely to receive concomitant antiplatelet therapy in comparison to controls (OR_{NL}: 6.91; 95% CI: 1.07-44.57, and OR_{IT}: 3.12; 95% CI: 1.36-7.17). UGI bleeding cases in UK were more likely to receive concomitant anticoagulants (OR: 2.56; 95% CI: 1.38-4.75), whereas no significant differences in anticoagulant use were observed between UGIB cases and controls in the Netherlands and Italy. From all UGI event cases in the UK, the Netherlands and Italy, respectively 11.7%,

11.8% and 32.4% had no documented UGI risk factor. The majority of cases were identified as having one or two documented UGI risk factors.

Across all three countries, most NSAID episodes were of short duration (i.e. less than 1 month), ranging from 53% in the UK to 85% in IT. The proportion of patients treated for 1-6 months ranged from 14% in IT to 29% in UK, while 0.9% to 19% of patients in the three countries were treated for more than 6 months. The median duration of coxib episodes was 30 days (interquartile range: 20-91 days) and median duration of nsNSAID +GPA (80% adherence) episodes was 28 days (interquartile range: 14-79 days).

Risk of UGI events and UGI bleeding

To compare the risk of UGI event between use of coxibs alone versus highly adherent nsNSAID+GPA use, a nested case-control study was conducted. From the adjusted model, no statistically significant decreased or increased risk was observed for nsNSAID + GPA users (80% adherence) as compared to coxib users (Table 2). This holds true for the three countries separately and as pooled estimates on patient level (Table 2). Regarding UGIB specifically, similar results were observed. For both outcomes, a trend towards a more protective effect for nsNSAID+GPA (80% adherence) as compared to coxibs was observed in the Netherlands and Italy (Table 2), but the adjusted model did not show a significant benefit (Table 2).

Meta-analysis of studies conducted at individual database-level using a random effects model (no significant heterogeneity between databases was shown, I-squared values of 0%) did not report different results from pooling on patient-level. Using this meta-analytic approach, adjusted ORs for UGI events and UGI bleeding following nsNSAID+GPA (80% adherence) compared to coxib use were 1.00 (95% CI: 0.73-1.33) and 1.11 (95% CI: 0.76-1.63), respectively.

Subgroup analyses

Stratification according to the predefined individual UGI risk factors was performed to identify a possible preference for either strategy in specific risk groups (Table 3). Since most cases of UGI events occurred in subjects aged 75 years and older, we performed additional analyses taking a different cut-off age of 75 years, which did not demonstrate different estimates from the cut-off of 65 years (data not shown). In non-antiplatelet users a non-significant increased risk both for UGI events and UGI bleeding was observed for nsNSAID +GPA (80% adherence), whereas the opposite was found for antiplatelet users. This interaction term was significant.

When we compared coxib use with highly adherent nsNSAID+GPA use in glucocorticoid users, the use of nsNSAID+GPA increased the risk for UGI events considerably (OR: 7.03; 95% CI 1.35-36.45)(P=0.020). When adjusting for the dosage of glucocorticoids, the estimated risk increased even more (OR: 9.01; 95% CI: 1.61-50.50)(P=0.012). Higher dosage of glucocorticoids affected the risk of UGI events more as a dose-response relationship was observed (data not shown). Regarding multiplicative interaction, the interaction term for use of glucocorticoids was not significant.

The withdrawal of rofecoxib from the market in 2004 influenced in general the prescription pattern of NSAIDs. After 2004 only celecoxib, etoricoxib, valdecoxib and parecoxib were available in Europe. Therefore, stratification according to time period was performed. A decrease in percentage of cases and controls using a coxib was noticed after rofecoxib was not available on the market anymore. However, this did not impact on the risk of an UGI event for nsNSAIDs+GPA versus coxibs (Table 3).

Discussion

In this case-control study we demonstrate that the risk of an UGI event or UGI bleeding is not different between users of non-selective (ns)NSAIDs in combination with adherent use of a gastroprotective agent (GPA) and coxib users.

Lowering the risk of NSAID-related UGI events can be achieved by concomitant use of GPAs. In particular increasing adherence to GPAs is important in reducing the risk nsNSAID-related UGI events.¹⁶⁻¹⁸ As another preventive strategy, COX-2- selective inhibitors were developed to improve the gastrointestinal safety of NSAID therapy, especially in high-risk patients such as elderly (aged ≥ 65 years) patients, those with a history of UGI events or concomitantly using anticoagulants, antiplatelets or corticosteroids. After the introduction of coxibs, it was shown that they indeed were associated with less gastrointestinal toxicity as compared to the traditional non-selective NSAIDs alone.^{11, 25-27} Several studies on this topic have been published in recent years.²⁸ Though the implementation of preventive strategies has increased in recent years, there is still room for considerable improvement with regard to use of preventive strategies during NSAID therapy.^{16, 29} In order to investigate which preventive strategy is superior with regard to UGI safety, head-to-head comparisons between coxibs and NSAIDs combined with GPAs have been performed in randomized studies. These studies showed no preference of one strategy over the other.^{5-7, 9-10} However, most clinical studies do not allow generalization of their results to daily clinical practice in Western countries, since many studies included selected categories of patients (i.e. high-risk patients with endoscopically documented UGI bleed/ulcer- or with specific disease, in particular rheumatoid arthritis), were performed in non-Caucasian persons, and in persons at very high risk of an UGI event.

Our results are in keeping with another observational study by Targownik et al. showing no superiority of nsNSAID combined with PPI use to coxibs in the prevention of NSAID-related UGI events.¹⁴ Although the efficacy of both preventive strategies overall seems equivalent for the upper gastrointestinal tract in the CONDOR study, the coxib-treated patients appeared to have a reduced risk of lower GI events as compared to nsNSAID plus PPI use.^{10, 30} However, results from other studies evaluating lower GI tract events as an outcome were conflicting.³¹⁻³⁴ A post hoc analysis of a prospective study showed a lower rate of serious lower GI events for rofecoxib compared to naproxen³⁰, whereas this was not confirmed in a cross-sectional capsule enteroscopy study showing comparable small-bowel damage between long-term NSAID and coxib users.³⁴ Mechanistically, whether the impact of NSAIDs on lower GI events reflect a reduction in risk by coxib-use or an increase in risk by PPI-use due to altered intestinal bacteria and increased susceptibility to small intestinal bacterial overgrowth is still under debate.³⁵ Another area of potential benefit of coxibs over nsNSAID plus GPA use might be in selected high-risk groups. In this study, we found that in glucocorticoid users, adherent use of an nsNSAID plus GPA was associated with a nine times higher UGI event risk compared to coxibs. This finding is supported by the dose-response relationship we observed where a higher dosage of glucocorticoids affected the risk of UGI events more than a lower dosage. The interaction term was not significant, but this is due to limited power since the estimates differed largely. To our knowledge, no previous study studied the comparison of coxib and nsNSAID plus GPA use in glucocorticoid users separately. Although data on glucocorticoids as an independent risk factor for UGI events are scarce, prior studies have shown a two-fold increased risk of UGI bleeding during glucocorticoid use alone.³⁶⁻³⁹ When glucocorticoids are used in combination with NSAIDs, the risk of UGI bleeding is estimated higher as compared to NSAID use alone or glucocorticoid use alone.³⁶⁻³⁹ Up to now, the reason for the interaction between both drugs has not been elucidated. One might speculate that glucocorticoids and NSAIDs act synergistically; experimental studies have shown that glucocorticoids inhibit the healing of

gastric mucosal damage⁴⁰⁻⁴¹ as well as NSAIDs do, although the mechanism of inhibition differs. Alternatively, gastric bacterial overgrowth due to acid-suppression such as occurs by PPI use⁴²⁻⁴³ might aggravate gastric mucosal damage by increased exposure time of gastric flora to the mucosal surface or by delayed gastric emptying caused by PPIs.⁴⁴ The combination of nsNSAIDs and PPIs therefore may have led to the observed increased risk in concurrent glucocorticoid users. As use of steroids is a risk factor that according to guidelines often will initiate GPA in NSAID-treated patients, this aspect is important to investigate in future studies.

Although not significant, we found a tendency towards an increased UGI event risk in patients with a history of an UGI event among nsNSAID plus adherent GPA users as compared to coxib users. In this particular high-risk patient group, one might consider the addition of a GPA to a coxib. This combination has been shown to reduce the risk of NSAID-related UGI events to a higher degree than coxibs alone or nsNSAIDs plus PPIs.¹⁴

In line with previous studies, concomitant use of low-dose aspirin seems to eliminate the UGI risk benefit of coxibs.^{12, 26-27, 45} Though not significant, we observed an increased UGI risk among nsNSAID plus adherent GPA compared to coxib users who did not concomitantly use aspirin, whereas the opposite was true for concomitant aspirin users. The interaction term was significant, pointing to an increase in risk of UGI events for coxibs when aspirin is used concurrently. In patients concomitantly using antiplatelets (including low-dose aspirin), GPAs should be recommended not only to nsNSAIDs users, but perhaps also to coxib users.^{3, 14, 19} The strength of the current study is the scale and setting: primary health care data from three European countries were combined reflecting real-life prescription patterns. Due to the setting it was possible to study both low-risk as well as high-risk patients. Previous evidence from clinical trials focused generally on high risk patients only.⁵⁻⁷

The following limitations should be acknowledged. By performing observational studies, certain biases can be introduced of which confounding-by-indication is the most important one to discuss. Confounding-by-indication could have been introduced as the general practitioner's awareness of the UGI risk profile of the individual patient might have influenced the prescribed preventive strategy. After the introduction of coxibs, high-risk patients were more likely to receive a coxib instead of co-prescription of a GPA to NSAIDs.⁴⁶ Nevertheless, the preference for preventive strategies changed after warnings for an increased cardiovascular risk related to coxibs were released by regulatory agencies.⁴⁷ Although the risk of UGI complications with rofecoxib used to be higher than with celecoxib⁴⁸, in a stratified analysis the estimate of nsNSAIDs plus GPAs compared to coxibs without rofecoxib after 2004 (i.e. celecoxib, etoricoxib, valdecoxib and lumiracoxib only) did not differ from the estimate including rofecoxib (before withdrawal). It is therefore unlikely that data on the use of rofecoxib prior to its withdrawal would have skewed the GI safety data in favor of the nsNSAID. We feel that it is therefore unlikely that the channeling away from coxibs for patients with cardiovascular disease would have led to important confounding.

We tried to address confounding-by-indication by matching on the number of UGI risk factors and by restricting the comparator group to nsNSAID users who were highly adherent to GPA (defined as at least 80% of nsNSAID days covered by a GPA prescription). Although crude incidence rates appeared to be equal between different levels of GPA adherence¹⁷, from previous studies we know that patients being adherent to the prescribed GPA are at the highest risk of nsNSAID related UGI events.¹⁷⁻¹⁸ Residual confounding due to exclusion of users with a lower GPA adherence level is therefore unlikely. In addition, we selected patient groups with a similar UGI risk profile, by matching on number of UGI risk

factors, as well as gender and age. Comparison between coxib and nsNSAID plus highly adherent GPA users showed no differences in number of UGI risk factors. Confounding was also dealt with by adjusting for several co-morbid conditions. The indication of glucocorticoid use could only be identified in the Netherlands, of which 64% was for rheumatoid disorders. Nevertheless, residual confounding cannot be ruled out in observational studies.

In addition, over-the-counter use of nsNSAIDs and GPA is not recorded in the databases and could have led to a potential underestimation of its use. We used drug prescription data rather than precise information on the actual use. Furthermore, the method of GPA adherence calculation used in the present study determined adherence based on days of GPA and of nsNSAID use, rather than daily coverage. However, we selected a group of highly adherent nsNSAID plus GPA users based on a cut off of 80% of GPA adherence.

In conclusion, there is no difference in the risk of UGI events between the use of coxibs and use of nsNSAIDs plus adherent GPA in daily clinical practice. Neither strategy was superior in the prevention of a first or a recurrent UGI event or UGI bleeding. A significant increase in the risk of UGI events for coxibs was observed when aspirin is used concurrently, whereas during concomitant glucocorticoid use nsNSAID plus GPA users are at increased risk of an UGI event compared to coxib users. Future studies on this topic are needed, as use of steroids is a risk factor that, according to guidelines, often will initiate GPA therapy in NSAID-treated patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Footnotes

Correspondence to: Gwen MC Maschlee, M.D. Dept. of Medical Informatics Erasmus University Medical Center PO Box 2040 3000 CA Rotterdam The Netherlands Phone: +31 10 7044116 Fax: +31 10 7044722 g.maschlee@erasmusmc.nl

Guarantor of the article: Gwen MC Maschlee

Author Contributions: Gwen MC Maschlee: acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis

Vera E Valkhoff: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis.

Eva M van Soest: study concept and design; acquisition of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision.

Giampiero Mazzaglia: acquisition of data; critical revision of the manuscript for important intellectual content

Mariam Molokhia: acquisition of data; critical revision of the manuscript for important intellectual content

René Schade: acquisition of data; critical revision of the manuscript for important intellectual content

Gianluca Trifirò: acquisition of data; critical revision of the manuscript for important intellectual content

Jay L Goldstein: acquisition of data; critical revision of the manuscript for important intellectual content

Sonia Hernández-Díaz: acquisition of data; critical revision of the manuscript for important intellectual content

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Abbreviations

ATC	Anatomical Therapeutic Chemical
BNF	British National Formulary
CI	Confidence Interval
COX	Cyclo-oxygenase
Coxib	Cyclooxygenase-2 inhibitor
GPA	Gastroprotective Agent
GPRD	General Practitioner Research Database
H₂RA	Histamine-2-receptor Antagonist
HSD	Health Search/CSD Longitudinal Patient Database
ICD-9-CM	International Classification of Diseases, 9 th Revision, Clinical Modification
IPCI	Integrated Primary Care Information database
NA	Not applicable
N adh	Non adherent
NSAID	Non-Steroidal Anti-inflammatory Drug
NsNSAID	Non-selective Non-Steroidal Anti-inflammatory Drug
OR	Odds Ratio
OTC	Over-the-counter
PPI	Proton Pump Inhibitor
UGI	Upper Gastro-Intestinal
UK	United Kingdom

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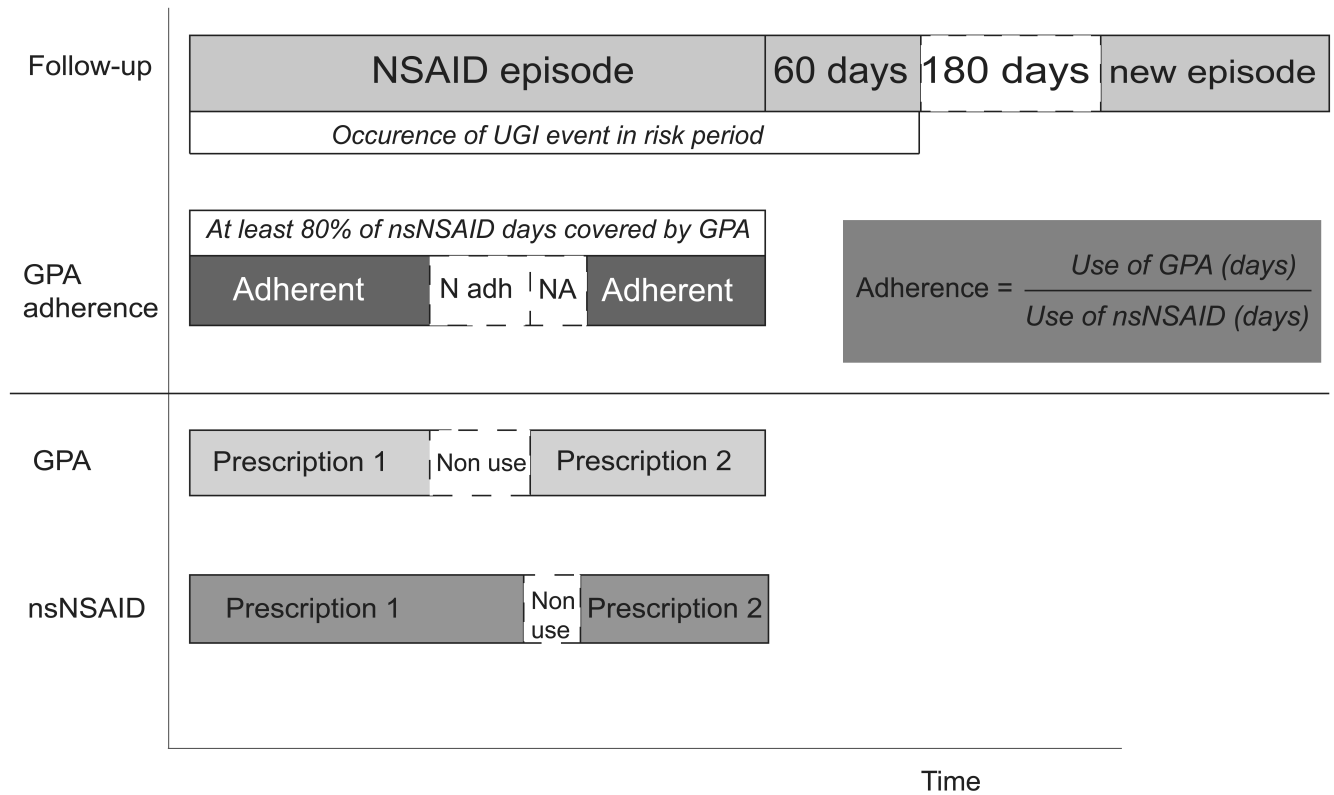


Figure 1.

Table 1
Baseline characteristics of cases with symptomatic UGI events (UGI bleeding and symptomatic ulcer) and matched controls by database.

	United Kingdom			The Netherlands			Italy		
	cases N=307	controls N=48,860	P- value	cases N=17	controls N=374	P- value	cases N=74	controls N=8,334	P-value
	n(%)	n(%)		n(%)	n(%)		n(%)	n(%)	
Age in yrs (mean±sd) *	74.0 (10.9)	71.2 (9.5)	NA	75.0 (9.6)	73.9 (9.7)	NA	69.9 (10.4)	68.5 (9.4)	NA
Age category: *			NA			NA			NA
50 – 64	60 (19.5)	12,222 (25.0)		2 (11.8)	63 (16.8)		26 (35.1)	3,385 (40.6)	
65 – 74	101 (32.9)	18,422 (37.7)		6 (35.3)	119 (31.8)		22 (29.7)	2,534 (30.4)	
75	146 (47.6)	18,216 (37.3)		9 (52.9)	192 (51.3)		26 (35.1)	2,415 (29.0)	
Gender (n(%) male) *	132 (43.0)	13,544 (27.7)	NA	5 (29.4)	71 (19.0)	NA	20 (27.0)	1,668 (20.0)	NA
UGI risk factors:									
Age 65 yrs	247 (80.5)	36,638 (75.0)	0.243	15 (88.2)	311 (83.2)	-	48 (64.9)	4,949 (59.4)	0.670
Prior UGI event	57 (18.6)	2,634 (5.4)	0.028	1 (5.9)	4 (1.1)	0.694	2 (2.7)	101 (1.2)	0.282
Use of antiplatelets	106 (34.5)	11,647 (23.8)	0.123	10 (58.8)	86 (23.0)	0.042	12 (16.2)	329 (3.9)	0.007
Use of anticoagulants	14 (4.6)	676 (1.4)	0.032	1 (5.9)	14 (3.7)	0.912	0 (0)	36 (0.4)	-
Use of glucocorticoids	18 (5.9)	1,298 (2.7)	0.289	0 (0)	11 (2.9)	-	3 (4.1)	98 (1.2)	0.143
Number of UGI risk factors: *			NA			NA			NA
0	36 (11.7)	10,578 (21.6)		2 (11.8)	61 (16.3)		24 (32.4)	3,300 (39.6)	
1	131 (42.7)	24,332 (49.8)		4 (23.5)	205 (54.8)		35 (47.3)	4,567 (54.8)	
2	112 (36.5)	13,310 (27.2)		10 (58.8)	103 (27.5)		15 (20.3)	455 (5.5)	
3	25 (8.1)	619 (1.3)		1 (5.9)	5 (1.3)		0 (0)	12 (0.1)	
4	3 (1)	21 (0)							
Other comorbidities:									
Dyspepsia	14 (4.6)	1,613 (3.3)	0.222	1 (5.9)	16 (4.3)	0.555	2 (2.7)	296 (3.6)	0.770
Smoking	252 (82.1)	39,153 (80.1)	0.272	4 (23.5)	54 (14.4)	0.599	3 (4.1)	278 (3.3)	0.714
Heart Failure	31 (10.1)	2,101 (4.3)	0.158	0 (0)	34 (9.1)	-	1 (1.4)	138 (1.7)	0.487
Diabetes mellitus	63 (20.5)	6,542 (13.4)	0.062	2 (11.8)	62 (16.6)	0.525	13 (17.6)	878 (10.5)	0.151
Concomitant use of other medication:									
SSRIs	34 (11.1)	3,071 (6.3)	<0.001	0 (0)	14 (3.7)	-	1 (1.4)	29 (0.3)	0.341
Spironolactone	5 (1.6)	391 (0.8)	0.423	0 (0)	6 (1.6)	-	(0)	(0)	-
calcium channel blockers	68 (22.1)	7,619 (15.6)	0.097	0 (0)	45 (12.0)	-	(0)	(0)	0.646
Duration of episode [#] :									
< 1 month	151 (49.2)	25,888 (53.0)	0.150	6 (35.3)	254 (67.9)	0.046	66 (89.2)	7,111 (85.3)	0.329
1-6 months	106 (34.5)	13,921 (28.5)	0.036	8 (47.1)	95 (25.4)	0.025	7 (9.5)	1,151 (13.8)	0.440
6-12 months	24 (7.8)	4,095 (8.4)	0.859	1 (5.9)	14 (3.7)	0.306	0 (0)	48 (0.6)	-
< 12 months	26 (8.5)	4,956 (10.1)	0.842	2 (11.8)	11 (2.9)	0.025	1 (1.4)	24 (0.3)	0.098

* Matching variables: age, gender and number of individual UGI risk factors.

SSRIs, selective serotonin reuptake inhibitors.

NA, Not applicable; matching criteria.

[#] Episodes of NSAID use were defined as consecutive NSAID prescriptions with intervening gaps not exceeding the duration of the previous NSAID prescription. The duration of an NSAID episode was calculated by dividing the prescribed quantity by daily dose regimen (United Kingdom/Netherlands) or the indication-specific defined daily dose (Italy). The end of an NSAID episode was defined as the end of the duration of the last NSAID prescription within that episode or the end of follow-up, whichever was earliest.

Table 2
The risk of symptomatic UGI events and UGI bleeding in users of nsNSAID+GPA (80% adherence) as compared to coxib users.

		Symptomatic UGI events (UGI bleeding and symptomatic ulcer)						UGI bleeding					
		Cases	Controls	ORmatch ed (95%CI)	P- value	ORadj [†] (95%CI)	P- value	Cases	Controls	ORmatch ed (95%CI)	P-value	ORadj [†] (95%CI)	P-value
		n (%)	n (%)					n (%)	n (%)				
United Kingdom	Coxib	128 (41.7)	24,722 (50.6)	1.00		1.00		86 (44.3)	14,835 (51.1)	1.00		1.00	
	nsNSAID+GPA [#]	179 (58.3)	24,138 (49.4)	1.02 (0.77-1.36)	0.883	1.05 (0.77-1.45)	0.742	108 (55.7)	14,222 (48.9)	0.90 (0.63-1.29)	0.568	1.20 (0.80-1.80)	0.375
The Netherlands [*]	Coxib	13 (76.5)	243 (65.0)	1.00		1.00		10 (71.4)	172 (60.4)	1.00		1.00	
	nsNSAID+GPA [#]	4 (23.5)	131 (35.0)	0.44 (0.13-1.48)	0.183	0.54 (0.16-1.84)	0.323	4 (28.6)	113 (39.6)	0.53 (0.15-1.88)	0.326	0.63 (0.18-2.24)	0.478
Italy	Coxib	44 (59.5)	6,201 (74.4)	1.00		1.00		6 (35.3)	1,124 (64.6)	1.00		1.00	
	nsNSAID+GPA [#]	30 (40.5)	2,133 (25.6)	1.22 (0.69-2.17)	0.500	0.79 (0.27-2.35)	0.673	11 (64.7)	616 (35.4)	2.85 (0.92-8.80)	0.069	0.59 (0.05-6.55)	0.669
Pooled on patient level	Coxib	185 (46.5)	31,166 (54.1)	1.00		1.00		102 (45.3)	16,131 (51.9)	1.00		1.00	
	nsNSAID+GPA [#]	213 (53.5)	26,402 (45.9)	1.01 (0.79-1.30)	0.918	1.02 (0.77-1.37)	0.880	123 (54.7)	14,951 (48.1)	0.96 (0.69-1.33)	0.800	1.14 (0.78-1.65)	0.503

Cases and controls are matched on age, gender and number of individual UGI risk factors.

^{*} For NL: adjusted model also includes use of antiplatelets.

[†] Adjusted for dose of NSAID, length of NSAID episode and density of NSAID use within episode. Only subjects included with known dosage of NSAID (UK 80.2%; NL 100%; IT 35.3%).

[#] nsNSAID+GPA (80% adherence)

Table 3
Risk factors for symptomatic UGI events (UGI bleeding and symptomatic ulcer) and UGI bleeding; stratified analyses on data pooled on patient level.

		Symptomatic UGI events (UGI bleeding and symptomatic ulcer)				UGI bleeding			
		Cases n (%)	OR _{matched} * (95% CI)	P-value	P-value Interaction terms	Cases n (%)	OR _{matched} * (95% CI)	P-value	P-value Interaction terms
Individual UGI risk factors:									
Age < 65 yrs	Coxib	34 (38.6)	1.00			11 (31.4)	1.00		
	nsNSAID+GPA [#]	54 (61.4)	1.01 (0.79-1.30)	0.918	0.055	24 (68.6)	1.61 (0.67-3.87)	0.291	0.466
Age ≥ 65 yrs	Coxib	151 (48.7)	1.00			91 (47.9)	1.00		
	nsNSAID+GPA [#]	159 (51.3)	0.88 (0.67-1.17)	0.394		99 (52.1)	0.88 (0.62-1.26)	0.488	
No prior UGI event	Coxib	171 (50.6)	1.00			93 (50.0)	1.00		
	nsNSAID+GPA [#]	167 (49.4)	0.98 (0.75-1.28)	0.877	0.152	93 (50.0)	0.86 (0.60-1.23)	0.397	0.417
Prior UGI event	Coxib	14 (23.3)	1.00			9 (23.1)	1.00		
	nsNSAID+GPA [#]	46 (76.7)	1.73 (0.81-3.70)	0.159		30 (76.9)	1.90 (0.74-4.86)	0.182	
No use of antiplatelets	Coxib	120 (44.4)	1.00			59 (41.0)	1.00		
	nsNSAID+GPA [#]	150 (55.6)	1.23 (0.91-1.66)	0.181	<0.001	85 (59.0)	1.24 (0.83-1.87)	0.298	0.008
Use of antiplatelets	Coxib	65 (50.8)	1.00			43 (53.1)	1.00		
	nsNSAID+GPA [#]	63 (49.2)	0.69 (0.44-1.08)	0.108		38 (46.9)	0.62 (0.34-1.06)	0.079	
No use of anticoagulants	Coxib	182 (47.5)	1.00			99 (46.7)	1.00		
	nsNSAID+GPA [#]	201 (52.5)	0.99 (0.76-1.27)	0.904	0.078	113 (53.3)	0.91 (0.65-1.28)	0.603	0.085
Use of anticoagulants	Coxib	3 (20.0)	-			3 (23.1)	-		
	nsNSAID+GPA [#]	12 (80.0)				10 (76.9)			

		Symptomatic UGI events (UGI bleeding and symptomatic ulcer)				UGI bleeding			
		Cases n (%)	OR _{matched} * (95% CI)	P-value	P-value Interaction terms	Cases n (%)	OR _{matched} * (95% CI)	P-value	P-value Interaction terms
Individual UGI risk factors:									
No use of glucocorticoids	Coxib	180 (47.7)	1.00			99 (46.5)	1.00		
	nsNSAID+GPA [#]	197 (52.3)	0.96 (0.74-1.24)	0.740	0.280	114 (53.5)	0.91 (0.65-1.27)	0.571	0.724
Use of glucocorticoids	Coxib	5 (23.8)	1.00			3 (25.0)	1.00		
	nsNSAID+GPA [#]	16 (76.2)	7.03 (1.35-36.45)	0.020		9 (75.0)	4.15 (0.72-24.01)	0.112	
Use of glucocorticoids ##	nsNSAID+GPA [#]	16 (76.2)	9.01 (1.61-50.50)	0.012		9 (75.0)	4.81 (0.79-29.20)	0.088	
Before rofecoxib withdrawal †	Coxib	162 (62.5)	1.00			91 (64.1)	1.00		
	nsNSAID+GPA [#]	97 (37.5)	1.05 (0.79-1.40)	0.729	0.702	51 (35.9)	0.92 (0.62-1.34)	0.649	0.781
After rofecoxib withdrawal ‡	Coxib	23 (16.5)	1.00			11 (13.3)	1.00		
	nsNSAID+GPA [#]	116 (83.5)	0.91 (0.57-1.47)	0.702		72 (86.7)	1.10 (0.56-2.15)	0.781	

* Matched on age, gender and number of individual UGI risk factors.

[#]nsNSAID+GPA (80% adherence).

^{##}Adjusted for equipotent dosage of prednisone (low dosage: 5 to 10 mg/day; moderate dosage: 10 to 20 mg/day; high-dosage: >20 mg/day)

[†]Rofecoxib withdrawal in September 2004, analysis until 2005.

^{*}Analysis from 2005 and subsequent years.